REMARKS

Status of the Claims

Claims 6 – 8 have been withdrawn. Claim 1 has been amended to clarify the selective effect of the method to induce the MPT in proliferating cells compared to non-proliferating or growth quiescent cells. The amendment is supported throughout the specification as filed, in particular, see page 24, lines 8 – 10. Claim 4 has been amended to correct an obvious typographical error. Claim 24 has been amended to incorporate the option for the As=O group to be replaced by an arsenoxide equivalent, as described in the application as filed at page 16, lines 15 – 16. Claim 27 has been corrected to be properly dependent on claim 24, as supported by page 16, lines 15 – 16 of the application as filed. Claims 24-26 have not been withdrawn as they are linking claims. Claims 1 - 5 and 9 – 28 are pending.

Rejection of Claims 1-4, 9-19, 23, 27, and 28 under 35 U.S.C. 103(a)

Claims 1-4, 9-19, 23, 27, and 28 stand rejected under 35 U.S.C. 103(a) for allegedly being obvious over the combination of Constantini (*Oncogene* **2000**, *19*, 307), Hogg (WO 01/21628) and Sawada (US Pat 5,270,196). Applicants respectfully traverse.

In the present action, the Office has alleged that Constantini teaches, (1) certain agents that are able to bind ANT induce MPT and thereby cause apoptosis; (2) said agents are useful as cytotoxic agents in the treatment of cancer; and (3) MPT is associated with cellular release of Cytochrome C. However, the Office admits that Constantini "does not teach the elected compound or the method further comprising determining whether the compound selectively induces the MPT in proliferating cells, relative to non-proliferating cells" (Line bridging pages 3 and 4 of the Office Action). To address this deficiency, the Office has cited the disclosure of Hogg for teaching the elected compound and its use in the treatment of proliferative diseases, including cancer. Further, the Office has cited the disclosure of Sawada for its teaching that, "a major problem with cancer chemotherapy is the non-specific action of anti-tumor agents which causes damage to normal growth quiescent cells and agents which selectively act on tumor cells are desireable." In light of the preceding, the Office has concluded that it would have been obvious to one or ordinary skill in the art at the time of the instantly claimed invention to practice the instantly claimed method.

As discussed below, the Office has not provided reasoning to combine the cited documents to yield the instantly claimed invention. Nor has the Office clearly shown that one skilled in the art at the time of the invention would have a reasonable expectation of success in indentifying any compound which selectively induce the mitochondrial permeability transition (MPT) in proliferating cells, relative to non-proliferating cells; that is, the Office has not shown that the results observed by the applicants were predictable.

The present invention relates to a process for identifying compounds which bind to the adenine nucleotide translocator (ANT) and **selectively** induce the mitochondrial permeability transition (MPT) in proliferating cells relative to non-proliferating cells.

Constantini merely presents a concept that a compound binding to ANT can induce the MPT and apoptosis, but it is silent with respect to any possible difference in the ability of ANT-binding-compounds to induce MPT in non-proliferating cells compared to proliferating cells. This is because at the time of the present invention, it was unknown to those of ordinary skill in the art that there existed a difference between proliferative and non-proliferative cells with respect to ANT induction of the MPT. Indeed, the present applicant tested one of the compounds of Constantini and found it was non-selective (see Example 4 of the present specification). Accordingly, it was unrecognized that ANT-induced MPT could be selectively triggered.

Hogg merely teaches that the elected compound is useful in the treatment of proliferative diseases including cancer but, like Constantini, does not teach or suggest that proliferative and non-proliferative cells differ with respect to ANT-induced MPT or that ANT-induced MPT could be selectively induced in proliferative cells. Hogg merely discusses decreased proliferation of cells treated by the compounds disclosed therein, but does not provide any information to suggest that an particular compound should be tested for affinity to ANT, that they would necessarily bind ANT, or that they would selectively induce MPT in proliferating cells.

Sawada merely notes a general problem with cancer chemotherapy being the non-specific action of anti-tumor agents which causes damage to normal cells, but is not concerned with ANT or MPT. Swada is merely an invitation to search for selective agents and provides no guidance that would lead one to the presently claimed invention. Its identification of the problem or need in no way suggests the presently claimed solution.

The combination of Costantini, Hogg, and Sawada fail to teach or suggest the underlying discovery that the MPT in proliferative and non-proliferative cells could be selectively induced in proliferative cells. Accordingly, the combination of Costantini, Hogg, and Sawada could not have taught or suggested that compounds that are able to selectively act to induce the MPT in proliferating cells relative to non-proliferating cells existed. Without such teachings or suggestions, the combination of Costantini, Hogg, and Sawada provide no reason for the ordinary artisan to seek out such compounds as presently claimed.

Furthermore, one skilled in the art, given the cited documents, would not have a reasonable expectation of success in identifying any compounds that selectively induce the mitochondrial permeability transition (MPT) in proliferating cells, relative to non-proliferating cells, by utilizing the presently claimed methods. Without the knowing the difference between proliferative and non-proliferative cells vis-à-vis ANT-induced MPT, the results observed and reported in the present application could not have been predictable.

In light of the preceding shortcomings of the cited documents, the present claims can not be considered obvious in light of the combination of Costantini, Hogg, and Sawada. Rather the instant claims yield unexpected and beneficial results. Accordingly, the applicants respectfully request reconsideration and withdrawal of this rejeciton.

Rejection of Claim 5 under 35 U.S.C. 103(a)

Claim 5 stands rejected under 35 U.S.C. 103(a) for allegedly being obvious over the combination of Constantini (*Oncogene* **2000**, *19*, 307), Hogg (WO 01/21628), Sawada (US Pat 5,270,196), and Cai (*Biochim. Biophys. Acta* **1998**, *1366*, 139). Applicants respectfully traverse.

Cai does not compensate for the deficiencies of Constantini, Hogg, and Sawada, noted above with respect to the present claims. That is, Cai also provides no teaching or suggestion that proliferative and non-proliferative cells differ with respect to ANT-induced MPT. Accordingly, The combination of Cai with Constantini, Hogg, and Sawada provides the ordinary artisan with neither a reason to make the claimed invention nor the reasonable expectation of success in doing so required to support an obviousness determination. Cai mererly provides disussion of a possible interconnection between generation of superoxide and cyt c release. Therefore, Applicants respectfully request reconsideration and withdrawal of the present rejection.

Conclusion

Reconsideration of this application is respectfully requested and a favorable determination is earnestly solicited. If it is believed that a teleconference will advance prosecution, the examiner is encouraged to contact the undersigned as indicated below.

Respectfully submitted,

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